An evaluation of machine intelligence tools to diagnose genetic diseases in critically ill infants

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Background

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55% disease of unknown etiology

Search for etiological diagnosis

Interim empirical treatment

Improvement or worsening

- Discharged home undiagnosed
- Delayed diagnosis: Anxiety, suffering
- Unnecessary morbidity and mortality
- Delayed palliative care
- Unnecessary cost

Treatment modification

Diagnostic and clinical utility of rapid whole genome sequencing

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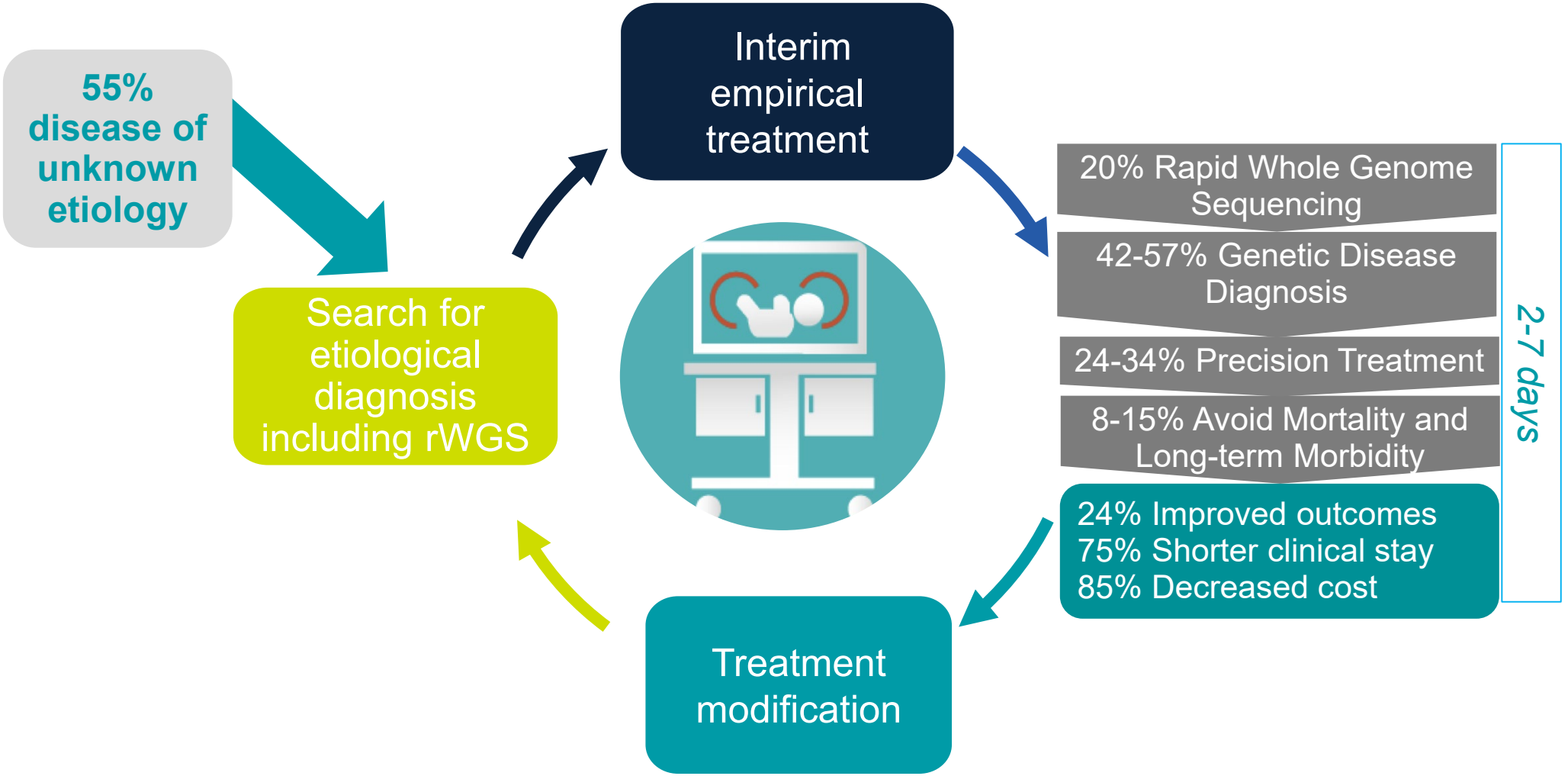
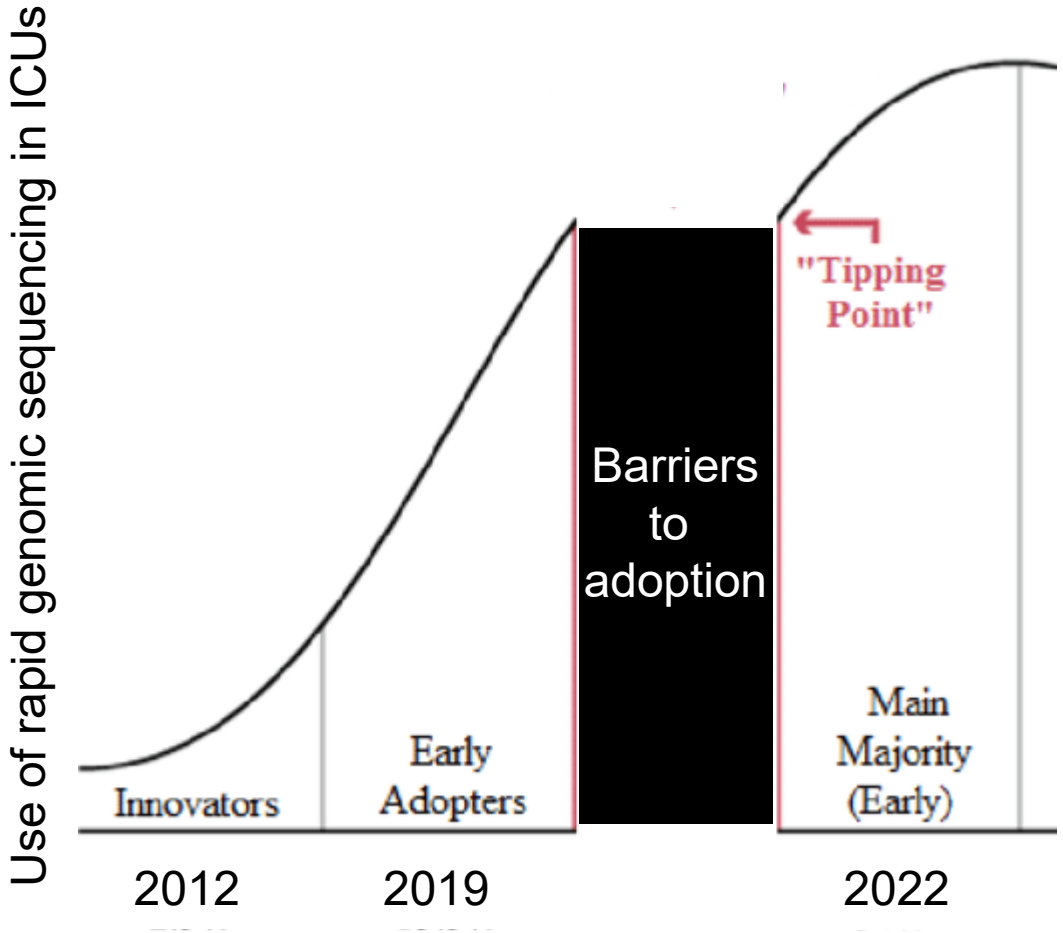


Barriers to broad adoption



- **Capital & labor intensity of rapid genomic sequencing**
  - **Shortage of expert medical geneticists, genetic counselors**
  - **Not scalable**
  - **Delays rapid changes in patient care**
- **Unfamiliarity with rapid genomic medicine**
  - **13,000 genetic diseases – most of them too rare to have been seen before by pediatricians**
- **Insufficient evidence of efficacy**
  - **Delayed authorization, failure of reimbursement**
- **Many genetic diseases lack effective treatments**
  - **Most treatments have not undergone rigorous testing**

Solution: automated diagnostic platform using machine intelligence

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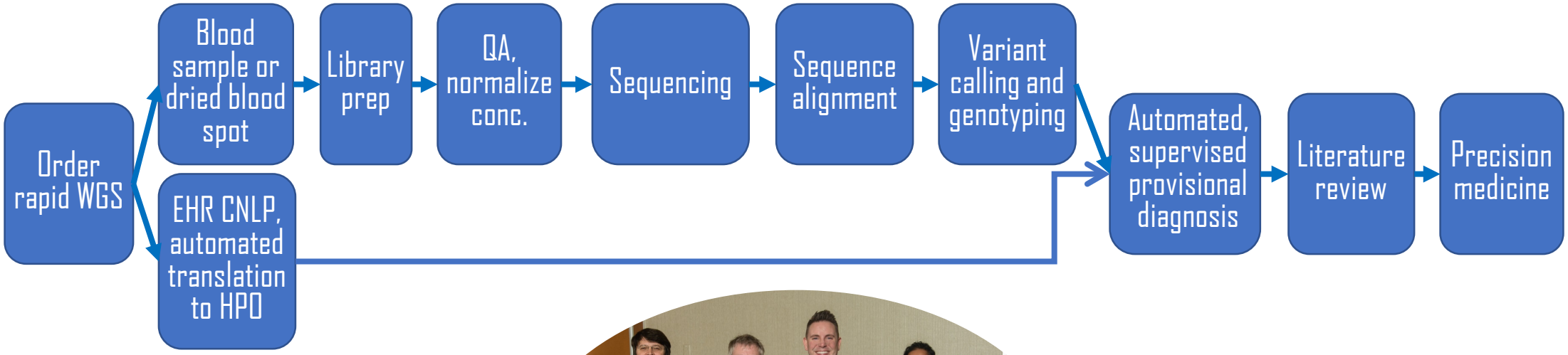

Time from blood draw to provisional diagnosis: 19.5 hours

Automated deep phenotyping

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Automated variant interpretation

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Evaluation of the automated diagnostic platform

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1. **Retrospective study – 84 children**
2. **Timed study – 10 children**
3. **Reanalysis study – 48 children**
4. **Prospective study – 50 children**

1. Performance in a retrospective cohort: 99% precision, 97% recall

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- **95 children with 97 genetic diseases diagnosed manually by rapid whole genome or whole exome sequencing with manually extracted phenotypes and manual interpretation**
- **Excluded incidental findings**
- **99% precision (93 of 94)**
- **97% recall (94 of 97)**

2. Timed study: 100% precision/recall
Mean time savings: 22hrs

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Use Type	Retrospective Patients				Prospective Patients													
Subject ID	263		6124	3003	6194		290		352		362		374		7052		412	
Age	8 days		14 years	1 year	5 days		3 days		7 weeks		4 weeks		2 days		17 months		3 days	
Sex	♀		♂	♀	♀		♂		♀		♂		♂		♂		♂	
Abbreviated Presentation	Neonatal seizures		Rhabdo-myolysis	Dystonia, Dev. delay	Hypoglycemia, seizures		Pulmonary hemorrhage, PPHN		Diabetic ketoacidosis		Neonatal seizures		HIE, anemia		Pseudomonal septic shock		Neonatal seizures	
Method	Auto.	Auto.	Auto.	Auto.	Auto.	Std.	Auto.	Std.	Auto.	Std.	Auto.	Std.	Auto.	Std.	Auto.	Std.	Auto.	Std.
Number of Phenotypic Features	51		115	148	14	2	257	4	103	4	65	1	112	6	124	3	33	1
Molecular Diagnosis	Early Infantile Epileptic Encephalopathy 7		Glycogen Storage Disease V	Dopa-Responsive Dystonia	None		None		Permanent neonatal diabetes mellitus		None		None		X-linked agamma-globulinemia 1		Benign familial neonatal seizures 1	
Gene and Causative Variant(s)	*KCNQ2* c.727C>G		*PYGM* c.2262delA c.1726C>T	*TH* c.785C>G c.541C>T	None		None		*INS c.26C>G*		None		None		*BTK* c.974+2T>C		*KCNQ2* c.1051C>G	
Sample/Library Prep (hours)	3:20	2:55	2:24	2:22	2:10	23:54	2:12	22:05	2:13	15:42	2:31	18:30	3:30	10:10	4:30	12:10	3:05	23:50
NovaSeq Loading (hours)	0:20	0:17	0:16	0:20	1:38	0:20	0:29	0:22	0:30	0:53	0:15	2:30	0:45	0:35	1:00	1:00	0:20	0:53
2x101 nt Sequencing (hours)	15:36	15:31	15:34	15:27	15:26	24:13	15:25	24:08	15:21	22:44	15:17	33:36	15:17	21:07	15:19	22:46	15:58	21:00
1^0 & 2^0 Analysis (hours)	1:03	1:02	0:59	0:59	1:07	3:05	1:00	1:57	1:01	2:30	1:02	2:30	1:02	2:30	1:09	2:25	1:24	2:24
3^0 Analysis Processing (hours)	0:06	0:05	0:07	0:05	0:06	0:15	0:08	0:14	0:06	0:15	0:05	0:15	10:28	0:16	0:06	0:16	0:06	0:16
Total (hours)	**20:25**	19:56	19:20	**19:14**	**20:42**	**56:03**	**19:29**	**48:46**	**19:11**	**42:04**	**19:10**	**57:21**	**31:02**	**34:38**	**22:04**	**38:37**	**20:53**	**48:23**

3. Reanalysis study: 4.2% diagnostic yield

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- **Automation of these reanalysis steps reduced the number of variants under consideration by an average of 99.9%.**
- **In two cases, diagnoses were made upon reanalysis, representing a yield of 4.2% (2 of 48).**
- **Four additional cases were flagged with a possible diagnosis to be considered during periodic reanalysis.**
- **An untrained analyst identified these six diagnoses with specificity = 0.83 and sensitivity = 0.76.**

4. Prospective performance: 100% recall

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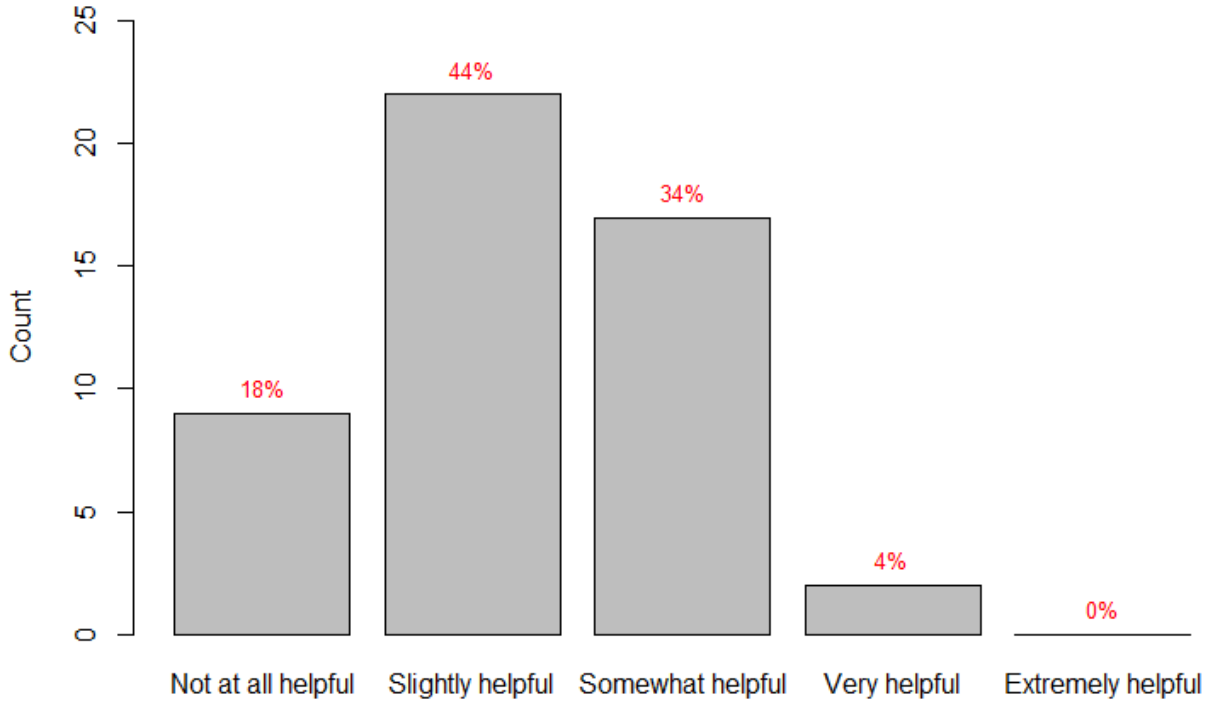
- **Out of 50 patients, the standard diagnostic workflow resulted in 16 (32%) diagnoses**
- **Automated analysis correctly diagnosed all 16 patients (100% recall)**
- **In addition to the standard workflow, analysts found automation to be very helpful in 4% of cases**

"How helpful was automated analysis in addition to the standard workflow?"



Rady Children's Institute for Genomic Medicine – the clinical lab perspective

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- **Hesitation when machine intelligence tools undergo rapid updates**
- **Goes against how clinical lab directors were trained to validate tools**
- **Need sufficient warning prior to updates**
- **Request increased transparency**

Moon's response to requests for transparency

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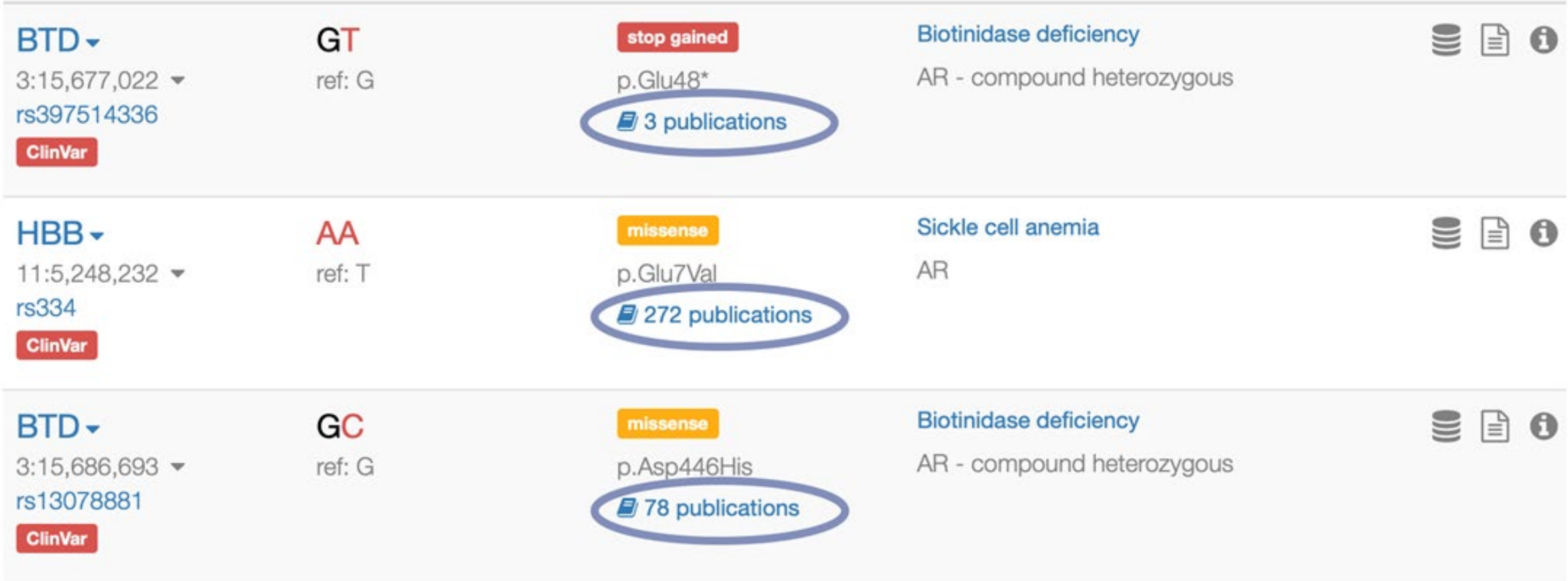

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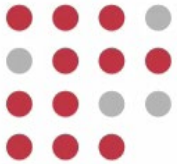
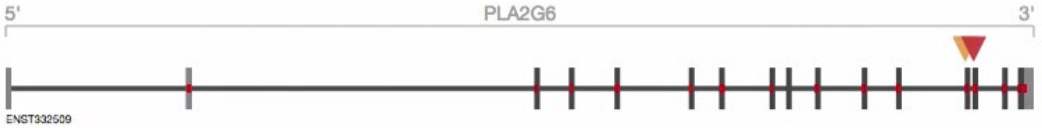
Effect

Transcript	Effect	p.notation	c.notation	Exon rank
ENST332509	missense	p.Arg591Trp	c.1771C>T	13/17
ENST335539	missense	p.Arg537Trp	c.1609C>T	12/16
ENST402064	missense	p.Arg537Trp	c.1609C>T	12/16

Protein prediction



Gene region



Frequency

0.0032% GNOMAD

0 HOMOZYGOTES

1 HETEROZYGOTES

0.0407% DIPLOID

Quality

77 DEPTH

37,40 ALLELE DEPTH

99 GENOTYPE QUALITY

Reported variants

Position	Genotype	Gene	Disorder
22:38511635	G/A	PLA2G6	Infantile neuroaxonal dystrophy 1
22:38512190	G/A	PLA2G6	Infantile neuroaxonal dystrophy 1

Variant discussion

PLA2G6 ▾ 22:38,511,635 ▾	GA ref: G	stop gained p.Arg645*	Infantile neuroaxonal dystrophy 1 AR	

Note

Two variants, a novel stop gained variant and a novel stop gained variant, were detected in heterozygous state in the *PLA2G6* gene (ENST332509: c.1933C>T; p.Arg645* and 332509: c.1933C>T; p.Arg645*). Parental DNA analysis is required to establish a compound heterozygous state of these two variants.

Mutations in *PLA2G6* have been shown to cause Infantile neuroaxonal dystrophy 1 (MIM: 256600), an autosomal recessive condition. The reported clinical phenotype of this patient overlaps with the manifestations of this condition regarding neurodegeneration, developmental regression, nystagmus, spastic tetraplegia, and cerebellar atrophy. The typical age of onset of Infantile neuroaxonal dystrophy 1 ranges from 0 to 10, which is in line with the reported age of onset in this patient (1 y.). Further clinical evaluation of the patient will give more insight into the phenotypic overlap with Infantile neuroaxonal dystrophy 1.

The detected variant causes stop gained. It is absent from gnomAD and absent from dbSNP, but has not previously been associated with disease. Parental DNA analysis (trio analysis) and DNA analysis of other (un)affected relatives, could establish co-segregation of this variant with the reported clinical phenotype.

Classification

Unassigned ▾

References

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The clinical lab perspective continued

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- **High sensitivity with automation, but unsure about sensitivity**
  - **Trust will come from large studies from other groups of hundreds of thousands of cases**
- **Development of publically available benchmarks to validate methods after every update**
  - **Example: Genome in a Bottle for clinical validation of genome sequencing**

Conclusion

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- **Although the automated diagnostic system is "hands-free", it's supervised at every step by expert bioinformaticians, clinical medical geneticists and clinical lab directors.**
- **May enable effective first-tier, provisional diagnoses or automated re-analysis of unsolved cases**
- **Wide-spread adoption would allow valuable cognitive resources of molecular laboratory directors and analysts to be reserved for difficult cases, manual curation of variants, and clinical report generation**

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